Computer models of endo-epicardial dissociation of electrical activity and transmural conduction during atrial fibrillation

❖ Valorization

AF importance and its economic burden

Atrial fibrillation (AF) is the most common sustained arrhythmia, occurring in 1–2% of the general population.[1] More than 6 million Europeans suffer from AF. The prevalence of AF is estimated to more than double in the next 50 years, as the population ages. AF confers a 5–fold risk of stroke and one in five of all strokes is attributed to this arrhythmia. The high morbidity and mortality associated with AF imposes substantial societal and healthcare cost burdens. Annual costs related to the management of AF patients in the European Union is roughly € 13.5 billion. [1]

So far several studies have been performed to understand the underlying mechanisms perpetuating AF. However, the results from these studies are not conclusive. Better understanding of the underlying mechanisms that contribute to AF would be beneficial for AF treatment. This would lead to higher life expectancy and a reduction in therapy cost.

The work in this thesis strongly supports the importance of one of the present mechanisms during AF called "loss of transmural connectivity between endocardium and epicardial layer" and helps the scientific community to understand better this mechanism. This mechanism plays an important role in highly complex AF dynamics and is an integral part of structural remodeling. The increase in endo–epicardial electrical dissociation increases AF complexity. An increase in AF complexity increases the number of coexisting waves and thus increases AF stability.

In abstract, these finding could be helpful in both pharmaceutical interventions and ablation strategies.

To whom are these research results of interest

In–silico cardiac models were mainly designed to understand or explain better the mechanisms underlying cardiac arrhythmias or diseases. Therefore, the main audiences in this field would be only academic community or researchers in this area. However, thanks

largely in part to the increase in computer powers, the current designed models in this field are becoming more and more sophisticated. Therefore, clinicians and biomedical companies can use the advantages of these models to test their designed algorithms or devices to detect or treat arrhythmias.
The 3D human atrial model presented in the chapter 6 of this study, is a good example of such models. The model could be used to simulate electrical activity on the anatomical realistic atrial without the interference of the ventricular electrical activity. Since this model was incorporated into an inhomogeneous torso model, the simulated atrial electrograms could be projected on the body surface and transesophageal leads. Several complexity parameters, such as dominant frequency and fibrillation wave amplitudes, could be extracted from simulated body surface electrograms in different degrees of fibrosis. These extracted complexity parameters could then be used to classify and characterize different AF conduction pattern complexities. This would be very beneficial for clinicians to detect and diagnose the AF and its stage.

How useful is this research for industry?

The presented research in this thesis is of interest for two industrial branches listed in below:

- **Pharmaceutical Companies**

Anti-arrhythmic drugs are still the main treatment option for AF. However, it is shown both experimentally and clinically that a drug such as Flecainide losses its efficacy in AF termination in the later stages of AF.[2] The role of computer models in this field of research has been to uncover the mechanisms for drug action or its efficacy loss. Aspects of this thesis investigated the possible mechanisms underlying this efficacy loss. The provided simulation results in this part has provided possible mechanistic explanations regarding the lower efficacy of Na-channel blockers treatment in patients in later stage of AF versus short term AF. These findings can be beneficial in pharmacological researches.

We also investigated the effect of fibrosis on fibrillatory conduction pattern complexity. For the upstream therapy these findings would be beneficial if it could prevent the loss of connectivity between the epicardial layer and the endocardial bundle network, e.g. by inhibiting fibrosis.

- **Clinics and Biomedical companies**

Another treatment option for AF is ablations. So far several ablation strategies were introduced and used clinically. Findings in our research strongly suggest that lesions created during ablation procedure should be truly transmural. This would in fact reduce the area available to fibrillation waves and should therefore strongly reduce AF stability.

How innovative is this research?

Based on our knowledge, the presented study is novel in the atrial fibrillation modelling area. The proposed models are the first modelling studies that were able to demonstrate transmural conductions during atrial fibrillation. Additionally, we were able to calculate endo–epicardial dyssynchrony with this model. Endo–epicardial dyssynchrony is a mechanism presents in later stages of AF and can have an important effect on AF stability. Using a realistic anatomical model, we also investigated the effect of transmural conduction on electrical conduction pattern complexity and its translation into body surface potentials.

Road to market

The ultimate product for cardiac modelling in the clinics should be patient specific models. A patient specific model is a tailor made computer model for each patient, based on his/her individual pathophysiological data.
Using a patient specific model, we can simulate AF for that specific patient and evaluate several therapy options specified for that patient. Most current medical diagnostic practices lead to rough

estimates of outcomes for a particular treatment plan[3] and their outcomes usually find their basis in the results of clinical trials. However, these results might not apply directly to individual patients[4] because they are based on averages.[5] Patient specific modeling can be used as an alternative approval tool to tailor treatment and optimize the treatment outcome for each individual patient.

In the past decade, patient specific modelling attracted more attention from both scientific groups and governmental funding agencies around the world. This is due to the fact that it has potential to improve diagnosis and optimize clinical treatments by predicting outcomes of the therapies and surgical interventions. [5]

In 2006, the European Union initiated a consortium 'Structuring the Europhysiome', that led to the Virtual Physiological Human (VPH) project. [6, 7] This project aims to stimulate research in the field of patient specific modelling for personalized and predictive healthcare and encompasses a number of more specific subprojects.[8] In November 2007, the National Institutes of Health (NIH) posted a Funding Opportunity Announcement regarding patient specific modeling (Predictive Multiscale Models of the Physiome in Health and Disease).[9] More recently, as a direct result of the American Recovery and Reinvestment Act of 2009, the National Institute of Biomedical Imaging and Bioengineering announced a challenge grant 'Towards the Virtual Patient', with the same goal as the prior NIH announcement.

Despite the attention, patient specific modelling still has a long way to go in order to become a standard of care in clinical practice. One possible explanation for this would be the lack of advanced technologies and mathematical algorithms in this area. Hence, many steps in the workflow from data acquisition to patient specific models still need to be performed manually. Additionally, the uncertainty in several electrophysiological parameters estimation for each patient is a huge obstacle. These parameters vary in each patient and they cannot be estimated non-invasively using current technologies.